NOTES ON THE TOXIC PROPERTIES OF THE BLOOD IN EPILEPSY.[1]

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Although the existence of a toxæmic element in the causation of epileptic seizures has repeatedly formed the leading topic of recent writers upon epilepsy there seem to have been no observations on the toxic properties of the blood of epileptic patients. With a view to obtaining some direct evidence as to the existence of such a toxæmic element I have made a number of experiments relative to the toxicity of the blood in epilepsy as measured by intravenous injections in rabbits. I shall refer briefly to the results of these observations in the hope that they may aid subsequent workers upon this difficult question.

The observations relate to the blood of fifteen epileptics at Craig Colony in the charge of Dr. Wm. P. Spratling and Dr. L. Pierce Clarke, to whose courtesy and coöperation I am indebted for the material and for the accompanying clinical histories. All of the fifteen patients have had grand mal seizures for several years. Owing to carelessness there is some uncertainty as to the identity of four of the patients whose blood was made the subject of study, and no attempt has been made to give histories of these cases. The method employed for determining the toxicity of the blood was that of intravenous infusion until the commencement of toxic symptoms. The rate of infusion was uniformly 5 cc. per minute. In four instances a second method was also employed, namely, that which consists in the intravenous injection of a much smaller amount of blood than is required to produce immediately toxic symptoms. Before speaking of the results of the infusions of the blood of our epileptic cases it is desirable to refer to the scope and limitations of the methods employed. Such reference is of the utmost importance, because there is frequently very great danger of misinterpreting the results of experimental injections of blood serum and of blood.

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When normal human blood serum is continuously infused at the rate of 5cc. per minute into the femoral vein of a rabbit, fatal tonic clonic spasms begin when from 20-40 cc. per kilo have been injected. The same serum may be distinctly more toxic to one rabbit than to another of the same weight. There is reason to think that serum from the same normal individual may vary in its toxicity at different times. Moreover, it is not always possible to say whether a person whose serum has been taken as a normal serum is really quite a normal person at the time of venesection, for it is conceivable that the presence of temporary derangement of digestion may in some degree influence the toxicity of the blood.

There are reasons which seem conclusive for thinking that the toxicity of normal human serum for rabbits depends on a proteid substance in the blood. In many instances it is found that at the very beginning of the convulsive seizures there are coagula in the heart and pulmonary vessels. The toxicity of normal serum has been attributed by Haymen and others to this property of inducing intravenous coagulation, but in a small proportion of cases I have been unable to find any evidences whatever of coagulation immediately after spasm had begun. It is not yet clear whether a marked increase in the toxicity of the blood above normal is always due to an increase of the coagulation-inducing properties of the blood or whether the increase may depend on other toxic influences.[2] The rate of infusion is a feature of considerable importance. In the observations recorded here the rate of 5 cc. per minute was employed. A slower rate, say of 2 cc. per minute, would have been preferable, as it would have required less blood to produce fatal symptoms. As already mentioned, the defibrinated blood was employed and not the serum of the blood. The difference in the toxicity of defibrinated blood and the corresponding serum probably depends entirely on the presence or absence of the red cells, the defibrinated blood being less toxic in proportion to the admixture with these cells. Thus the approximate serum toxicity of the blood may be estimated by regarding it as about 50 per cent. greater than that of defibrinated blood. Judged by this standard it is seen that of the fourteen cases in which the toxic values of the serum were determined by the method of rapid infusion these were normal in at least 12 instances. Of the two apparent exceptions one relates to a patient whose history was lost. The other exception relates to the case numbered 2, in which the seizures seem to be closely related to over-eating and are often associated with prolonged headaches, with congestion of the face and conjunctivæ. In this case the quantity of blood required to produce fatal symptoms was only 15 cc. to the kilo, which is equivalent to about 10 cc. of serum. This is a distinctly higher toxic value than that of normal serum. The observation just mentioned was made with blood drawn in the interval between two seizures. Another observation made about one month later, while the patient was suffering from a congestive headache following over-eating, gave no indication of increased toxicity of the blood, the values falling probably within normal limits.

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[2] It is now well known that the injection of an alien serum into the circulation of the rabbit may lead to the destruction of many red blood cells, with resulting hæmoglobinuria. Small quantities of serum do not cause sufficient destruction of red cells to cause hæmoglobinuria. In the observations referred to in the paper, hæmoglobinuria was not noted in any instance. In the case where rapid infusion was employed the animals lived much too short a time to develop hæmoglobinuria.

In four instances an effort was made to determine the toxic values of the blood by means of a second method as well as by the one described. This method is also one of intravenous infusion, but instead of infusing until fatal symptoms are initiated, an attempt is made to determine the minimum dose that will prove fatal in from 12 to 36 hours. This is the method generally employed in the study of the toxicity of blood serum. It is open to the objection that it may be necessary to make the infusion into several rabbits in order to make certain that the minimum quantity necessary to kill has been discovered, but is upon the whole a reliable method. The fatal dose of normal serum is usually regarded as varying from 8-12 cc. to the kilo of the animal's weight. Of the four trials referred to, the toxic values were apparently above the normal in two (Nos. 2 and 4). In one of these (No. 4) there is a want of correspondence between the result obtained by the first and that obtained by the second method, the value for the first method being well within normal limits. The other case is the one already referred to as characterized by congestive headaches. As with the first-named method, it is seen that there is an indication of exaggerated toxic properties of the blood during the interval between seizures. The quantity of the blood which killed a rabbit weighing 1800 gm., i. e., 10 cc., failed to kill a rabbit weighing 1750 gm. when taken from the patient during the congestive state. It is also to be noticed that on the occasion of the first trial with this patient's blood there was extensive clotting in the cavities of the heart and veins, whereas clotting was much less pronounced, or was entirely absent, on the occasion of the second trial.

In three instances the toxicity of the blood was tested immediately after a grand mal seizure, and then again after intervals of 15, 16½ and 26 hours respectively, in the three cases. In one case the blood appeared more toxic at the second bleeding than at the first, in another more toxic at the first bleeding than at the second, and in the third about equally toxic on the two occasions.

Two further observations deserve brief mention. In one of these (No. 4) the blood taken three weeks after a seizure and two weeks before another was infused into a dog. The effects upon the animal were simply those which are observed from the infusion of normal blood in large volume.

The other observation was made with blood drawn 15 days after a seizure and several days before another. This blood was infused into the femoral vein of a Java monkey weighing 1200 gm. The quantity introduced was very large, 145 cc. The symptoms produced (mainly dyspnœa and cyanosis) were those which follow the infusion of a large volume of normal human blood into the circulation, and death was wholly referable to the mechanical action of the infused blood.

If we look over the data which form the basis of this report with a view to seeing what they teach us about the toxic properties of the blood in epilepsy, it is clear that no positive conclusions can be reached. In all of our cases, except one, the evidence indicates that the toxicity of the blood was not increased, or that the results of different infusions are contradictory. The criticism might be made that the blood of certain of our epileptic patients may have contained toxic substances whose presence would not be indicated by the use of so crude a method as that employed. I am disposed to think that such a criticism would be entirely just. Although the method suffices to indicate that in pneumonia and uræmia the toxicity of the blood may be markedly increased, it is probable that it would fail to indicate slight variations from the normal toxicity. Hence it can only be said that the evidence, such as it is, does not indicate any increase in the toxic properties of the blood of most cases of epilepsy, either immediately after the seizures or in the intervals.

As regards the one case in the series in which the blood appears to have been distinctly more toxic than normal in an interval between the paroxysms, no positive conclusion can be reached. It is possible that this increase in the toxic action of the blood may be in some manner connected with the disorders of digestion, dependent on indiscretions in diet, which are characteristic of this patient. It is possible that the blood of normal persons may temporarily be increased in toxicity under similar conditions of disordered digestion.

In conclusion, it may be said that the chief purpose of this report is to call attention to the very great difficulties that attend the investigation of the toxic properties of the blood in epilepsy. These difficulties are largely the result of the crude nature of the available methods of study, which are poorly adapted for the detection of slight differences in the toxic values of blood, although they have given important results in the investigation of the well-defined toxæmias of pneumonia, uræmia and scarlet fever. Those shortcomings may, however, be in some degree lessened by the use of certain precautions in using known methods, and the following suggestions are made for the consideration of those who undertake further researches upon the toxicity of the blood of epileptics:

First: In testing the toxicity of the blood by rapid and continuous infusion into the circulation of rabbits the rate of infusion may advantageously be limited to 2 cc. per minute, and the infusion should be stopped when the first indications of involuntary spasm appear. It is desirable that the weight of the rabbits employed should not vary beyond certain fixed limits—say 1400-1600 gm., and that all the animals should be of the same breed.

Secondly: The method just mentioned should be controlled by means of the method which has for its object the determination of the minimum intravenous injection that causes death in from 12 to 36 hours. At least three observations should be made by this method for each

Name.	Rate. c.c.	Quantity. c.c.	No. of c.c. to Kilo.	Weight of Rabbit.	Symptoms.	Remarks.
No. 1—C. K. Bled 3.30 p.m. Dinner at noon.	5	48 8	32 5.25	1500 1520	Contracted pupils, tonic clonic spasms. Recovered.	
No. 2—C. W. Bled 3 p.m. Dinner at noon. Dec. 30, '97.	5	26 10	15 5.50	1740 1800	15 c.c., pupils contracted. 20 c.c., cyanosis and dyspnœa. 26 c.c., tonic clonic fibrillation. Drowsiness in a few minutes. Died in 45 minutes in spasms.	Extensive clotting in veins and heart.
Jan. 28, '98. In congestive state. Dinner at noon. 3 p.m.	5	95	55	1710	5 c.c., pupils slightly contracted. 25 c.c., twitching face and nose. 80 c.c., eyeballs prominent. 95 c.c., severe tonic clonic spasm.	Moderate clotting.
	5	52 10	32 6	1650 1750	20 c.c., pupils contracted. 52 c.c., spasm and death. Recovered.	No clotting in heart.
No. 3—W. D. M. 3 p.m. Dinner at noon.	5	35 15	30 11	1180 1335	5 c.c., contracted pupils. 35 c.c., tonic clonic spasms. Died in 40 minutes. Slight spasm in legs.	Extensive clotting in four chambers of heart and pulmonary veins.
No. 4—W. H. J.	5	70 20	37.68 9.32	1845 2145	Pupils slightly contracted. No spastic symptoms. Died in 15 or 20 minutes. Very drowsy. No spasms.	No thrombi of heart or vessels. No thrombi in heart or vessels.
8 days after seizure.		50	24.75	2020	Dyspnœa and cyanosis.	General clotting.
10 days after seizure.		45	40.72	1105	Dyspnœa and cyanosis.	General clotting.

3 weeks after seizure.	5	40	31.19	1205	Severe spasms and death.	
" "		110		Dog 10 k.	Breathing slow and deep. Lived 48 hours.	
4 weeks after seizure.		20	14.5	1380	Small pupils. Rapid breathing. Lived 24 hours.	
No. 5—A. H. No seizure for 6 days.	5	68	43.09	1578	Contracted pupils at 50.	Extensive clotting.
No. 6—A. H. No seizure in 4 days.	5	45	25.14	1790	25 c.c., contracted pupils.	Clotting.
No. 7—N. J. No seizure for 7 days.			22.77	1537	Died with usual symptoms, 35 c.c.	
No. 8—B. C. No seizure for 15 days.	5	45	51.42	875 Java monkey	Contracted pupils. Drooping lids—after 100, cyanosis. No spasm at any time. No clotting. Patches of œdema and congestion in lungs. No congestion of intestine.	
		145		1200		
No. 9—A. W. Grand mal seizure 2.45 p.m. Bled 3.30 p.m.	5	105	36.2	2900	Usual symptoms. Symptoms begin at 50.	
15 hours after seizure.	5	100	52.63	1900	70 c.c., pupils slightly contracted.	
No. 10—C. S. Seizure 6.55 p.m.	5	90	50	1800		
Bled 7.35 p.m.	5	50	27.77	1800	Fibrillation marked.	
26 hours later.	5	38	20.76	1830		
No. 11—K. A. Seizure 4.30 p.m. Bled 5.15 p.m.	5	90	43.9	2050	Symptoms at 60.	
" 16½ hours after seizure.	5	65	46.42	1400	Symptoms as above.	

sample of blood, and the average of the toxic values should be taken. The results may be depended on if there is an agreement between the indications of the methods.

Thirdly: When practicable the toxicity of the serum for guinea pigs should be determined by subcutaneous injection, as recently suggested by Uhlenhuth, working with Brieger. This method has the advantage of obviating the effects of intravenous coagulation.

Fourthly: Should there be cases where the toxicity of the blood appears regularly to be increased near the time of seizures it would be well to make a further test by intravenous infusion into monkeys. In these animals intravenous coagulation seems not to be induced by human blood. Moreover, this animal's means of expression are so perfected that slight toxic effects appear to be more readily discernible in him than in other animal types.

To carry out studies as thus suggested is laborious, and requires the use of large quantities of blood, but I am convinced that reliable physiological evidence as to the toxic properties of the blood in epilepsy cannot be obtained except through laborious and numerous observations. It is likely that some chemical alterations in the blood, not without pathological significance to the organism, could be entirely overlooked even with the use of the most painstaking methods of physiological inquiry.

No. 1.—C. K., 32. Occupation, farmer. Paternal grandmother died of phthisis. Two sisters died of kidney disease (?). His epilepsy began at the age of 29; supposed to have been due to rheumatism, patient having suffered from an attack of acute articular rheumatism and pericarditis some two years prior to his first epileptic fit. About one half of his attacks are grand mal in character; the others are of psychic type. At the time of admission to the Colony, patient suffered from temporary glycosuria, which lasted for several weeks. Albumin in small quantities was also present in urine. This condition rapidly disappeared after having been placed upon anti-diabetic diet. Although patient has had frequent severe attacks since absence of sugar in the urine was noted, yet he has never had a return of this functional phenomenon.

No. 2.—C. W., 18. Occupation, housework. Father has at times been intemperate. Mother died of phthisis. Epilepsy began in infancy and was supposed to have been caused by "heart disease." Attacks are almost all grand mal in character, occurring by day, and are preceded by a feeling of dizziness and pain in the epigastrium. Heart shows mitral regurgitation. Patient has an abnormally large appetite and has frequently eaten inordinate quantities of food and vomited on several occasions soon after. At times preceding her attacks, and occasionally at other times when no attacks follow, she has suffered from prolonged congestive headaches. The face is red and the conjunctivæ are congested; the face bears the appearance of one coming from the hot room of a Turkish bath. At times patient has been placed upon restricted diet and reduced some twenty or thirty pounds in weight, with marked improvement in her seizures and entire abolition of her congestive headaches. Whenever she is allowed to return to the regular dietary she immediately regains her former stout physical condition and her seizures return to their former frequency and severity.

No. 3.—W. M., 40. Occupation, merchant. Patient's relatives for several generations have at times been somnambulic. Maternal grandmother died of epilepsy. Patient's father died of brain fever. Epilepsy began at the age of 34. It is supposed to have been caused by prolonged dissipation and generally dissolute life. Attacks are both grand mal and petit mal. Patient is frequently automatic after both kinds of attacks and is occasionally violent for several days. Attacks are all preceded by epigastric aura. He has suffered from considerable mental deterioration since his epilepsy began. Frequently, prior to his attacks for two or three days, his face is markedly congested, conjunctiva injected, and pulse is hard, wiry and increased in frequency.

No. 4.—W. H. J., 25. Occupation, farmer. Mother died of cancer of the breast. Patient's epilepsy began at the age of 18 and is supposed to have been caused by an injury to the head by a tree falling upon him about six months prior to first fit. Attacks are almost all grand mal in character. For the past two years, since patient's admission to the Colony, he has suffered from periodic attacks of mental stupor, in which his general appearance is that of melancholia cum stupore or acute primary dementia. In these states, which are not at all regular, patient loses greatly in bodily weight and bed sores frequently form in various parts of the body, apparently as a result of pressure and mal-nutrition. One examination of the blood conducted in this case was made between his periods of stupor when he was about the Colony daily at work.

No. 5.—A. H., 27. Occupation, seamstress. General neurotic history among paternal relatives. Maternal grandfather markedly intemperate. A younger brother is feeble-minded. Epilepsy began at the age of 14. Her mother suffered from considerable mental stress just prior to the patient's birth, and the labor was very difficult and performed by the aid of instruments. No cause was assigned for her epilepsy. Attacks at first were petit mal, but are now grand mal in character; they are frequently followed by automatism and occasionally considerable mental disturbance precedes and accompanies a series of attacks. No aura. Patient is quite feeble-minded.

No. 6.—A. H., 24. Occupation, housework. Mother has had severe headaches for years, and father has had rheumatism the greater part of his life. Patient's epilepsy began at the age of 14. No cause was assigned. Attacks are almost all grand mal in character and usually occur at night, preceded by no aura and followed by marked mental depression. Considerable mental deterioration has taken place. Heart, mitral regurgitant murmur. Knee-jerks atypically active. Several times since patient's admission to the Colony she has suffered from temporary eczema of either the right or the left hand, which condition immediately improved under topical treatment and proper management of the dietary, especially when nitrogenous food was withdrawn.

No. 7.—N. J., 24. Occupation, housework. No neurotic history obtainable. Epilepsy began at the age of 12. Assigned cause of epilepsy was overstudy at school. First attack occurred at the first menstruation, which appeared to be normal. Her attacks are almost all grand mal in character and are preceded by no aura. Patient is in very good mental health. She very frequently suffers from acute exacerbation of chronic eczema, which is quickly controlled and removed by proper attention to the dietary, and especially when placed upon milk diet exclusively.

No. 8.—B. C., 28. Occupation, housework. Patient's father died of paralysis (?). Mother died of cancer of the uterus. Patient's epilepsy began at the age of 17; cause ascribed to mental worry and an overdose of toothache medicine. Attacks are almost all grand mal in character and generally occur in series, preceded by an aura consisting of a sensation of numbness in the fingers of the left hand. At times patient has led a variable life and has been subject to sexual excesses since epilepsy began. Reflexes uniformly atypically active. Patient almost always suffers from marked mental depression following her seizures and considerable disorder in alimentation.

No. 9.—A. W., 24. Occupation, housework; epilepsy existent since 12 years of age, although patient had quite a number of eclamptic convulsions at dentition. No neurotic family history was obtainable, except that the father was very intemperate and died from alcoholic excesses. At the age of 10, patient had cerebral palsy, leaving left side hemiplegic. The supposed cause of epilepsy was this hemiplegia. Aura, mental confusion. Mind somewhat enfeebled. All reflexes of left side are markedly exaggerated. Almost all attacks are grand mal.

No. 10.—C. S., 27. Occupation, farmer. No neurotic history obtainable. Epilepsy supposed to have begun at age of 17, although patient had many convulsions at dentition. Supposed cause, abnormal dentition. Almost all attacks are grand mal. Aura, muscular trepidation in the calves of both legs for two or three minutes prior to convulsion. Patient is in very fair mental condition. He has frequently complained of severe and prolonged headaches and general mental depression some days prior to his convulsions.

No. 11.—K. A., 32. Occupation, housework. No neurotic history obtainable. Epilepsy began at the age of 13. Supposed cause, severe fright. Convulsions are almost all of grand mal type and of the most violent kind, the tonic and clonic stage often lasting for five or ten minutes. Mind somewhat weak. Patient is often very irritable just before and after seizures. Knee-jerks uniformly atypically active. Pupils dilated.

20. Ein Fall von progressiver Paralyse bei Mutter und Kind (A Case of General Paresis in Mother and Child). O. Müller (Allgemeine Zeitschrift f. Psychiatrie, 55, 1898, p. 151).

The author here presents the clinical and pathological histories of two cases of general paresis occurring in a child of eleven, and in the mother at the age for forty-five.

There was a neurotic family history, and the mother had syphilis. One younger child died at an early age, of convulsions, said to have been caused by congential syphilis. The mental affection first was present in the daughter, who up to the age of ten or twelve was a promising young girl. The first symptoms noted were those of inability to skate well, the girl having been quite an adept in this pastime. The writing soon became affected, and the girl commenced to be left behind in her classes as a result of her gradually increasing dulness which advanced to a complete and helpless dementia. The mother began to be affected a few years later than the daughter. Her first symptoms were of the nature of extreme jealousy. Later she became very indolent and careless of her person, began to drink freely, and unmindful of her household duties. Paresis of the muscles of articulation was an early symptom, and the disease progressed in typical fashion.

The post mortem examinations showed the generally received lesions of general paresis in both cases.